REMARKS

In the official action of 20 June 2007, claims 1, 4-9, and 16-25 are pending and were examined. Claims 1, 4-9, and 16-25 are rejected under 35 U.S.C. §103(a) as allegedly obvious. Claims 1, 4-9, 16-21, and 25 are rejected under a nonstatutory obviousness-type double patenting rejection as allegedly obvious.

Claims 1, 4-9, and 16-25 are pending after entry of this amendment. Claims 1, 4-9, and 16-25 have been amended. No new matter has been introduced as a result of the amendments herein.

Support for the amendments to claim 1 lies in the specification at least at page 3, lines 10-14, 25, and 29-32 and page 4, lines 25-26.

Claim 4 has been amended for clarity. Support for the amendments to claim 4 lies in the specification at least at page 2, line 27 through page 3, line 6.

Claims 5-9 and 16-25 have been amended for clarity. Support for these amendments lies in the preceding versions of claims 5-9 and 16-25.

Reconsideration in view of the claim amendments and following remarks is respectfully requested.

Rejection of claims 1, 4, 5, 7, 16, 18, 21 and 25 pursuant to 35 U.S.C. §103(a)

Claims 1, 4, 5, 7, 16, 18, 21 and 25 are rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of Felberbaum et al. (1997) or Albano et al. (1996) or Engel et al. (1997) or Olivennes et al. (1994), in view of Ziegler et al. (1998) in further view of Hall et al. (1991). Official action, pages 3-10.

Specifically, it is alleged that it would have been obvious for one of ordinary skill in the art to perform the claimed invention because the four alternative primary references (Felberbaum et al., Albano et al., Engel et al., and Olivennes et al.) are alleged to teach methods for the therapeutic management of infertility by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof; suppressing premature ovulation by

administering a LHRH antagonist during the follicular phase of a treatment cycle; inducing ovulation by administering HCG; and applying assisted reproduction techniques (steps (b)-(e) of the preceding version of claim 1). Official action, pages 3-5.

As stated by the examiner, none of the primary references teach programming the start of controlled ovarian stimulation by administering a LHRH antagonist during the luteal phase of the menstrual cycle. Official action, bottom of page 5. However, it is alleged that Ziegler et al. teach the desirability of permitting the advanced timing of the onset of controlled ovarian hyperstimulation (COH) by administering a compound (*e.g.*, oestradiol) during the luteal phase. Official action, page 6. It is further alleged, that while none of the aforementioned references teach advance timing by administering an LHRH antagonist, Hall et al. remedies this deficiency. Official action, page 7. It is alleged that Hall demonstrates that administration of GnRH antagonist NalGlu in the mid-luteal phase results in luteolysis and shortening of the luteal phase, and that these alleged teachings viewed in combination with one another render claim 1 obvious. Official action, page 9. It is also alleged that the features set forth in claims 4, 5, 7, 16, 18, 21 and 25 are either disclosed by one or more of the above references or are obvious in view of the combination of the references in further view of the knowledge of one of ordinary skill in the art for the reasons discussed in the official action.

The burden is on the examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co*., 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc*., 550 U.S. __, 82 USPQ2d 1385 (2007), the U.S. Supreme Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (USPTO Guidelines) state that, having undertaken the factual inquiries of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements

according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (5) variations that would have been predictable to one of ordinary skill in the art; and (6) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007).

Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the examiner must consider objective evidence that rebuts such predictability and reasonable expectation of success. This objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id*. When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at __, 82 USPQ2d at 1396.

The applicants submit that the examiner fails to make a *prima facie* case of obviousness because the factual inquiries set forth in *Graham v. John Deere Co*. have not been considered. Having undertaken such an objective analysis, the applicants further submit that the cited references fail to render claims 1, 4, 5, 7, 16, 18, 21 and 25 obvious given that none of the rationales identified by the U.S. Supreme Court in *KSR* apply. Specifically, the elements of the present claims are not found in the prior art cited, or are not substitutions of other known elements. Accordingly, rationales (1) and (2) of the USPTO Guidelines do not apply. The claims are arguably directed to the improvement of methods for classical COS/ART procedures, but rationales (3)-(6) of the USPTO Guidelines, or other rationales, require predictability in the

art and/or a reasonable expectation of success, which is lacking from the teachings of the cited references. Specifically:

(1) Claim 1 has been amended to encompass a method of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART), the method comprising the following steps:

a) programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle,

wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix, and further wherein the LHRH antagonist is administered at a dosage range between 0.5 mg to 10 mg;

b) terminating administration of the LHRH antagonist prior to the onset of menses;

c) programming controlled ovarian stimulation by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof, during the follicular phase of the programmed menstrual cycle;

d) suppressing premature ovulation by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the follicular phase of the programmed menstrual cycle;

e) inducing ovulation by administering HCG; and

f) applying assisted reproduction techniques;

(2) Claims 4, 5, 7, 16, 18, 21 and 25 all depend from claim 1;

(3) the scope and content of the prior art did not describe a method comprising programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle and terminating administration of the LHRH antagonist prior to the onset of menses;

(4) the instant invention provides a method comprising programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle, terminating administration of the LHRH antagonist prior to the onset of menses; and

(5) at the time of the instant invention, one of ordinary skill in the pertinent art would not have reasonably concluded that the claimed methods could be performed with a reasonable chance of success given the deleterious or disruptive effects of gonadotropin deprivation caused by LHRH antagonists on the physiological and biochemical processes required for oocyte development and that it was unknown how administration of LHRH antagonists during the luteal phase would affect ovarian stimulation and reproductive endocrine feedback mechanisms in infertile patients.

As stated by the examiner, none of the primary references (Felberbaum et al.. Albano et al., Engel et al. and Olivennes et al.) teach programming the start of controlled ovarian stimulation by administering an LHRH antagonist during the luteal phase of the menstrual cycle and terminating the administration of the LHRH antagonist prior to the onset of menses (as recited in steps (a)-(b) of claim 1).

Ziegler et al. fail to remedy the deficiencies of the primary references. Ziegler et al. describe an alternative to classical COS/ART procedures set forth in claim 1, steps (c)-(f). Ziegler et al state that among their objectives is to "provide a more physiological approach to multiple follicular stimulation and possibly improve the outcome of COH and its outcome while diminishing the overall need for HMG or recombinant FSH" (*see* page 562, left hand column). Thus, Ziegler et al expressly teach away from the classical COS/ART procedures set forth in claim 1, steps (c)-(f).

Further, Ziegler et al. fail to teach or suggest that an "advanced timing method" can be accomplished by administration of LHRH antagonists in the preceding menstrual cycle, as set forth in claim 1, step (a). In fact, Ziegler et al state that their approach "provides the practical

advantage of permitting an advanced timing of the onset of COH treatments when gonadotrophin-releasing hormone agonists are not used" (*see* Abstract).

Further still, Ziegler et al. teach administration of a compound (*e.g.*, oestradiol valerate) starting on day 25 (or ~ 3 days before anticipated menses) of the preceding (i.e. luteal phase) menstrual cycle until the first Tuesday following menses (see page 562 left hand column, last paragraph). Thus, Ziegler et al. fail to teach or suggest termination of administration of an LHRH antagonist, or any putative "advanced timing compound", prior of the onset of menses at set forth in claim 1, step (b). Programming of controlled ovarian stimulation according to the claimed methods relies upon the induction of menstrual bleeding, as this indicates the preparation of the uterine endometrium and low oestradiol values. Consequently, the duration of the growth of the newly developing follicle(s)/oocyte(s) and the timing of oocyte pick-up and embryo transfer can be calculated.

Hall et al. also fail to remedy the deficiencies of the primary references and Ziegler et al. Hall et al. examine the differential sensitivity of the ovary to temporary withdrawal of gonadotropin support by administering an LHRH antagonist (Nal-Glu) to women with normal menstrual cycles and without any evidence of infertility. Hall et al. is not concerned with programming a COS/ART cycle with follow-up administration of an LHRH antagonist in the follicular phase for the prevention of a premature LH surge/ovulation in infertile patients.

Hall et al. report that treatment of patients with LHRH antagonists in mid-follicular phase (MFP) studies resulted in a prolongation of follicular phase length by 9 days (see page 995, right hand column). Similarly, treatment of patients with LHRH antagonists in late-follicular phase (LFP) studies resulted in a total cycle length increased by 6 days. Accordingly, one of ordinary skill in the art would conclude that administration of an LHRH antagonist during the luteal phase results in a disturbance in hormones and endocrine regulation system that would not only fail to promote COS/ART programming, but would be counterproductive. Thus, Hall et al. also teach away from the instant invention.

The observations of Hall et al. further reinforce what was known and would be expected in the art at the time of the instant invention. For example, LHRH antagonists were considered to be capable of compromising the mitotic program of cells undergoing folliculogenesis, blastomere formation and endometrium development by inhibiting the synthesis of growth factors and through direct interactions with the LHRH receptor (*e.g.*, *see* the abstract of Hernandez, 2000, Human Reproduction 15(6):1211-1216). LHRH antagonists were also considered to be capable of interfering with mechanisms involved in germinal vesicle breakdown and the cell signaling pathway driving the oocyte into metaphase II (*e.g.*, *see* De la Fuente et al, 1999, Human Reproduction, 14: 3060-3068).

The examiner rebuts the applicants' previous arguments by alleging that the primary references (Felberbaum et al.. Albano et al., Engel et al. and Olivennes et al.) demonstrate that LHRH antagonists are safe and effective for use with assisted reproductive techniques. Official action, pages 17 and 18. To the contrary, none of the cited references demonstrate safe and effective use when LHRH antagonists are administered in the luteal phase of the preceding menstrual cycle. Administration of LHRH antagonists during the follicular phase does not contradict what was known in the art at the time of the instant invention, and administration of LHRH antagonists during the follicular phase is part of many classical COS/ART procedures.

Thus one of ordinary skill in the art would expect that administration of an amount of LHRH antagonist during the luteal phase sufficient to induce luteolysis and the start of menses could have deleterious effects on oocyte meiosis and the mitotic programs of cells undergoing folliculogenesis, blastomere formation and endometrium development during the following cycle. Thus there would be no expectation that LHRH could be administered safely during the luteal phase of a menstrual cycle for the purposes of programming COS/ART in the following menstrual cycle.

Based upon the foregoing, the applicants assert that, prior to the instant invention, the subject matter of claims 1 was neither described or could be reasonably predicted by one skilled in the art. Claims 4, 5, 7, 16, 18, 21 and 25 depend on claim 1. Thus, the examiner has not established a *prima facie* case and withdrawal of the rejection of claims 1, 4, 5, 7, 16, 18, 21 and

25 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. is respectfully requested.

Rejection of claims 6, 8, 9, 17, 19, and 20 under 35 U.S.C. §103(a)

Claims 6, 8, 9, 17, 19, and 20 are rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of in view of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. as applied to claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-25, and in further view of U.S. Patent No. 5,945,128 to Deghengi or Rabasseda (1999).

Deghengi is alleged as teaching that cetrorelix, teverelix, ganirelix, and antide were known to be the LHRH antagonists.

Rabasseda is alleged as teaching that LHRH antagonists such as cetrorelix, ganirelix, and abarelix were known to be useful for treating female infertility.

As discussed above, at the time the invention, the primary references did not disclose or suggest the method set forth in claim 1 or any of the rejected claims depending therefrom. Both Deghengi and Rabasseda, viewed either alone or in combination, fail to remedy the deficiencies of the primary references because neither Deghengi nor Rabasseda discloses or suggests inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of a menstrual cycle preceding a programmed menstrual cycle and terminating administration of the LHRH antagonist prior to the onset of menses or demonstrates the safe and effective use thereof in programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART). Further, one of ordinary skill in the art would not be motivated to modify the teachings of the primary references by looking to either Deghengi or Rabasseda to program the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle and terminate administration of the LHRH antagonist prior to the onset of menses, because one of ordinary skill in the art would expect such a

treatment would have deleterious effects both incompatible and counterproductive to programming COS/ART procedures. One of ordinary skill in the art would expect no different result simply by selecting specific LHRH antagonists disclosed in Deghengi or Rabasseda. Accordingly, the examiner has not established a *prima facie* case and withdrawal of the rejection of claims 6, 8, 9, 17, 19, and 20 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. and in further view of Deghengi or Rabasseda is respectfully requested.

Rejection of claims 1, 4-9, 16-21 and 25 under Obviousness-Type Double Patenting

Claims 1, 4-9, 16-21 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 ("the '192 patent") of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and Kent.

In order to make a non-statutory obviousness-type double patenting rejection, the '192 patent and instant application must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3). Further, the claimed subject matter must either be anticipated by, or merely an obvious variation of, the subject matter claimed in the '192 patent. With respect to this latter requirement, the examiner alleges claims 1, 4-9, 16-21 and 25 are obvious variants of claims 1-6 of the '192 patent. Official action, pages 14-15. As such, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination. MPEP 804. Specifically, the examiner alleges that the claims of U.S. Patent No. 6,319,192 and the instant application only differ in that the instant claims set forth a programming step, and that in view of the alleged teachings of the prior art previously discussed, the instant claims would be obvious to one of ordinary skill in the art at the time of filing.

Both the '192 patent and instant application have at least one common inventor and are commonly owned. Claims 1-6 of the '192 patent encompass methods of therapeutic management of infertility by intrauterine insemination consisting of dose-dependent suppression of endogenous gonadotropins with an LHRH antagonist, exogenous stimulation of ovarian follicle growth, ovulation induction with HCG, native LHRH, LHRH agonists or recombinant LH, and intrauterine insemination by sperm injection.

However, instant claims 1, 4-9, 16-21 and 25 encompass methods of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART), the method comprising the following steps:

a) programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle,

wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix, and further wherein the LHRH antagonist is administered at a dosage range between 0.5 mg to 10 mg;

b) terminating administration of the LHRH antagonist prior to the onset of menses;

c) programming controlled ovarian stimulation by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof, during the follicular phase of the programmed menstrual cycle;

d) suppressing premature ovulation by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the follicular phase of the programmed menstrual cycle;

e) inducing ovulation by administering HCG; and

f) applying assisted reproduction techniques.

As noted by the examiner, the claims of the '192 patent fail to set forth any programming steps (i.e. programming the start of a programmed menstrual cycle and controlled ovarian stimulation). While the prior art may allegedly teach that such programming is desirable, neither

the '192 patent, nor any of the prior art cited and previously discussed, claims, discloses or suggests inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of a menstrual cycle preceding a programmed menstrual cycle and terminating administration of the LHRH antagonist prior to the onset of menses or demonstrates the safe and effective use thereof in programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART). As discussed previously, at the time of filing, one of ordinary skill in the art would expect that performing the claimed methods would have deleterious effects that are both incompatible and counterproductive to programming COS/ART procedures. Accordingly, withdrawal of the rejection of Claims 1, 4-9, 16-21 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and Kent is respectfully requested.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: 20 December 2007

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